GPCRs Regulate DNA Integrity

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G protein-coupled receptors (GPCRs) and their associated signaling proteins represent one of the most diverse cellular signaling systems involved in both physiological and pathophysiological processes. Aging represents perhaps the most complex biological process in humans and involves a progressive degradation of systemic integrity and physiological resilience. This is in part mediated by age-related aberrations in energy metabolism, mitochondrial function, protein folding and sorting, inflammatory activity, signal transduction fidelity and genomic stability. An increased rate of unrepaired DNA damage is considered to be one of the key 'hallmarks' of aging. Over the last two decades our appreciation of the complexity of GPCR signaling systems has expanded their functional signaling repertoire. One such example of this is the incipient role of GPCRs and GPCR-interacting proteins in DNA damage and repair (DDR) mechanisms. Emerging data now suggest that GPCRs could function as stress sensors for intracellular damage such as oxidative stress. Given this role of GPCRs in the DNA damage response process, coupled to the effective history of drug targeting of these receptors, this suggests that one important future activity of GPCR therapeutics is the rational control of DNA damage repair systems.

Keywords: G protein-coupled receptor (GPCR) ; aging ; DNA damage ; β-arrestin ; G protein-coupled receptor kinase (GRK) ; interactome ; G protein-coupled receptor kinase interacting protein 2 (GIT2) ; ataxia telangiectasia mutated (ATM) ; clock proteins ; energy metabolism

1. Introduction

With the knowledge gained about mechanisms underlying health and disease, as well as improved living standards and sanitization, there has been a major increase in the global average lifespan [1]. The World Health Organization reported in 2019 that an estimated 703 million people were aged 65 or older. This number is expected to double by 2050 (United Nations, Department of Economic and Social Affairs, Population Division (2019). World Population Ageing 2019: Highlights (ST/ESA/SER.A/430)). Despite this positive result of improved healthcare, a major complication incurred with this increase in the size of the worldwide elderly population is the burgeoning prevalence of aging-related diseases including neurodegenerative disorders, cardiovascular diseases and diabetes mellitus [2]. This has been borne out through multiple studies connecting age-related molecular pathologies and the incidence of these disorders [3][4][5]. These reports have suggested that the aging process itself is an underlying cause for multiple diseases; however, aging itself is not considered a disorder, but a normal physiological process [2]. Pathological aging can be defined as a progressive deterioration of physiological functions, which will eventually lead to systemic dysfunction and death [2]. These pathophysiological alterations include metabolic dysfunction, genome instability, telomere attrition and oxidative stress [6][7]. A greater understanding of these processes should improve our capacity to prevent or treat age-related diseases [8].

Transmembrane heptahelical GPCRs represent perhaps the most studied and effective drug targets to date. Their near ubiquitous role in physiological processes, coupled to their capacity to recognize a wide diversity of impinging molecules, makes them ideal targets for pharmacotherapeutic design [9][10]. As a testament to the functional efficacy of targeting GPCRs in disease, 475 drugs (~34% of all drugs approved by the FDA, acting on over 108 unique GPCR targets) are currently clinically employed [9]. While currently dominating the realm of therapeutics, there is still a strong impetus for future GPCR-based drug design. There are over 300 new experimental drugs that are currently in clinical trials, of which ~20% target 66 previously unexploited GPCR systems. The major disease indications for GPCR modulators have shown a trend towards diabetes, obesity and Alzheimer disease (AD), all of which are strongly age-dependent disorders. While the majority of the worldwide drug design effort has been made using the concept of exploiting and controlling the G protein-dependent signaling modality of GPCRs, there is now a growing field of more 'engineered efficacy' therapeutics that can utilize alternative modes of non-G protein-mediated GPCR signaling [11][12][13]. The emergence of these new and diverse GPCR signaling modes expands our concepts of the types of signaling systems that can be controlled through GPCR modulation. Here we will investigate one of these new target systems that may hold the key to the future treatment of multiple age-related disorders [14][15][16][17], *i.e.* the DNA damage-response (DDR) system.

As life proceeds through the individual's aging process, both endogenous (*e.g*. reactive oxygen species (ROS)) and environmental (*e.g*. ionizing radiation) stressors are constantly attacking DNA, causing structural damage [8]. Unrepaired DNA damage negatively affects genome replication and transcription, causing wide-scale chromosomal aberrations that disrupt critical cell functions such as energy metabolism and protein folding/management [18][19][20]. Given the importance of DNA-protective activity as an anti-aging strategy, coupled to the feasibility of GPCR druggability, the generation of GPCR-based DDR controlling agents holds considerable promise for improved treatments for both disorders of genomic aging such as Werner syndrome or Ataxia-Telangiectasia, as well as age-related disorders such as Metabolic Syndrome or Parkinson's disease.

2. G Protein-Coupled Receptor Systems: Intersections with aging and senescence

2.1. GPCR Signaling Diversity

The GPCR superfamily forms one of the largest and most diverse groups in the human proteome [21]. Different GPCRs interact with extremely divergent chemical compounds ranging from photons, neurotransmitters, small metabolites to complex hormones and exogenous animal toxins. Thus the GPCR superfamily encompasses a broad range of cellular sensory systems that allows tissues to sense and adjust to diverse endogenous and environmental perturbagens. GPCRs are unique in their structural and functional diversity and have been therapeutically exploited to effectively combat a plethora of diseases.

Even though GPCRs are most structurally distinct in the orthosteric ligand-binding site, they show the most conservation in the transducer site [22]. In other words, GPCRs interact with disparate extracellular ligands, but elicit a typical intracellular response observed across the GPCR superfamily. All GPCRs bind heterotrimeric G proteins consisting of αβγ subunits (Gαβγ) and can induce a G protein signaling cascade. There are 16 Gα, 5 Gβ and 13 Gγ subunits in humans, which allows many different aggregations and signaling outputs [23]. The responses reach from activation to inhibition and are classified based on the downstream function of the α subunits into four families, Gαs, Gαi/o, Gαq/11, and Gα12/13 [24]. Classical G protein signaling is induced through ligand stabilization of the heptahelical core to create an active tertiary structure and induces conformational changes in the intracellular loops and the carboxyl terminus. In a reverse manner, the binding of G proteins to receptors exerts an allosteric effect on the ligand binding region and increases the agonist binding affinity [25]**.** The ligand-activated receptor conformation promotes binding of the Gαβγ and triggers the exchange of GDP for GTP on the α subunit. In essence GPCRs act as ligand-activated guanine nucleotide exchange factors. G protein nucleotide exchange facilitates the dissociation of the heterotrimeric G protein in its GTP-bound α subunit and the free βγ dimer. Both subunit groupscan then activate intracellular downstream effectors, such as ion channels or enzymes, and thereby amplify the signal for cellular activities. The GTP-bound α subunit triggers its cognate effectors such as the cAMP catalyzing enzyme adenylyl cyclase, inositol 1,4,5-phosphate (IP3) or phospholipase C. The free βγ dimer also shows modulatory activities on downstream effectors, *e.g*. promoting the interaction of G protein-coupled receptor kinase (GRK) with GPCRs which then phosphorylates the C-terminus or intracellular loops of the GPCR. The phosphorylation facilitates coupling to β-arrestin and directly affects GPCR function by desensitization [26]. The α subunit is inactivated by cleaving GTP to GDP and eventually recombines with the βγ subunit and terminates its activity.

In addition to this G protein signaling mechanism data gathered in the last two decades points towards additional non-G protein signaling activities of GPCRs [27][28][29][30][31][32]. The discovery that these additional signaling pathways are therapeutically tractable, such as the β-arrestin mediated signaling cascades suggests that additional drug design avenues may be fruitful. Luttrell et. al demonstrated that β arrestin mediates SRC family kinase recruitment and is critical for the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) pathways [11]. Apart from the primary association of β-arrestin with GPCR internalization and desensitization [33], they appear to form complexes with the inactivated receptor and other scaffolding proteins that evoke GPCR associated signals [27]. β-arrestins have been demonstrated to bind a wide variety of kinases, e.g., E3 ubiquitin ligases, phosphodiesterases and transcription factors [34]. More recently it has been shown that β-arrestin activation through β2-adrenergic receptors (β2AR) augments DNA damage, p53 degradation and apoptosis under chronic stress conditions [35]. Therefore, targeting β2AR and attenuating β-arrestin signaling might be an attractive target to support DNA damage repair mechanisms.

Multiple lines of research have recently focused on the conceptual modelling of GPCRs contend with the possibility of employing signaling preferences between G protein or β-arrestin signaling, known as signaling 'bias'. GPCRs likely exist in a set of multiple conformational states (which can be then stabilized by distinct ligands) [36] associated with the preferential activation of certain pathways [31]. Shifting of the equilibrium constants between these multiple states is likely to be the basis of therapeutically relevant drug effects - an improved understanding of the complex GPCR activity landscape will hopefully augment our ability to design signal-selective therapies [37]. The topology of this activity

landscape is likely to be a product of the capacity of GPCRs to form ‘higher-order’ stable receptor protein complexes [30][36]. These large multiprotein complexes are often described as ‘receptorsomes’. It is likely that ligands evoke a range of signaling outputs between G protein and non-G protein signaling - these actions can either take place sequentially via pluridimensional signaling complexes or simultaneously via the concurrent activation of more dedicated and restrictive signaling complexes [38]. The signaling outcome is likely determined by G protein activity and the expression profile of additional proteins involved in creating stable receptorsome complexes [39]. Further extending the appreciation of GPCR signaling complexity is the additional contextual basis of signaling diversity via variance in subcellular localization. GPCR research for many years has focused on the molecular species present on the cell surface at the plasma membrane. The majority of GPCR copies in the cell however reside in multiple intracellular compartments - initially thought to act as a reserve supply only for the cell surface species. Initial research demonstrating how subcellular localization could specify discrete signaling activities emanated from investigations into receptor endocytosis [40][41][42][43]. While the endocytic modulation of GPCR signaling still involved cell surface GPCR species, multiple specifically intracellular environments have now been shown to be important sites of signaling diversification, e.g. mitochondria, endoplasmic reticulum, Golgi apparatus and nucleus [44][45]. This additional signaling capacity proposes that GPCRs interact with intracellular stimulatory factors - or even deleterious factors such as reactive oxygen species - to transduce their full signaling repertoire. This concept therefore strongly suggests that GPCRs might act as molecular sensors for compounds that directly or indirectly induce oxidative stress and/or DNA damage [32].

While many researchers often view signal transduction complexity as a hindrance to therapeutic development, in fact it is a positive aspect as the added nuances of signal transduction actually facilitate the rational creation of multiple distinct biased agents. Indicative of this capacity for exploitation of signaling complexity therapeutically-relevant signaling bias has already been shown for several receptors including, the GnRH receptor [46], chemokine receptors [47], the parathyroid hormone receptor [30] and the neurotensin-1 receptor [48].

2.2. GPCR Functionality in the Context of Molecular Gerontology

Aging is a time-dependent functional decline characterized by the accumulation of cellular damage leading to a progressive loss of physiological integrity [49]. Accordingly, aging is a major risk factor for chronic metabolic disorders such as obesity, type 2 diabetes and cardiovascular disease [50]. Part of the aging process involves loss of homeostatic balances leading to redox imbalances, impairment of oxidative phosphorylation and accumulation of dysfunctional mitochondria [51]. Systemic metabolic dysregulation, including mitochondrial dysfunction, is a key hallmark of aging. The dysregulation results in elevated levels of reactive oxygen species (ROS) and sustained oxidative DNA damage, requiring activation of DNA damage repair mechanisms [52][53]. This causes adverse changes in cells over time, increasing vulnerability to developing nearly all diseases [54].

From a signal transduction perspective GPCRs can be seen as the master regulators of somatic tissue functions - the other side of this physiological coin however implicates GPCRs in the etiopathophysiology of a wide range of human diseases. Inter-connected GPCR systems allow highly specific inter-organ crosstalk, making up a complex neuroendocrine control network that regulates ‘neurometabolic’ activity [55]. Via the regulation of a diverse range of G protein-dependent and non-G protein signaling modalities GPCRs possess a potent capacity to control intermediary cell metabolism events (*e.g.* kinase activation or calcium mobilization) as well as transcriptional and translational efficacies [55][56][57][58][59][60]. Therefore, as GPCR systems are likely involved (via a diverse range of activities) in the broadest range of physiological functions their importance in the regulation of the aging process is unsurprising. It is highly likely that one of the most important nexi within this GPCR-aging axis is the functional interplay at the level of genomic integrity control and the DDR process. Molecular aging causes accumulating protein and DNA damage and can also generate age-related increases in cellular senescence. Many stimuli, both intra- and extracellular, can elicit a senescence response. These include dysfunctional telomeres, DNA damage, the expression of certain oncogenes, perturbations to chromatin organization and strong mitogenic signals [51][61]. Many of these stimuli are signaled by pathways that overlap in activating the tumor suppressor protein 53 (p53) and upregulate the cyclin-dependent kinase (CDK) inhibitors p21 and p16 [50][62].

2.2.1 GPCRs and the DNA damage repair process

We have recently demonstrated that multiple components of the GPCR signaling system can modulate the activity of signaling proteins directly or indirectly involved in DNA damage and/or repair [63][64][65]. From its relatively recent inception [66] aging research has focused strongly on the links between energy metabolism and age-related damage [67][68]. Disruption of the glucose metabolic system is nearly universal in aging and as this primary metabolic process falters, a negative energy balance occurs, as ATP levels reduce while reactive oxygen species (ROS) levels increase. The simultaneous loss of the capacity to maintain energetic processes in the face of increasing oxidative stress will eventually

overwhelm cellular antioxidant capabilities, resulting in oxidative damage of DNA. Many age-related disorders that affect our population, such as neurodegeneration, type 2 diabetes mellitus (T2DM) and cardiovascular disorders, are caused by these hallmarks [2].

Stress-induced DNA damage is arguably the most prominent underlying cause of aging and in turn may be one of the primary players in almost all age-related disorders [69]. This hypothesis has been supported by the investigation of accelerated aging disorders, *i.e.* Hutchinson–Gilford progeria syndrome, Ataxia Telangiectasia and Werner syndrome, which have one commonality, they are a direct effect of DNA damage response (DDR) and repair disruption [70][71][72][73][74].

Stress-induced DNA damage can occur at the level of whole chromosome structures, as well as to exposed single- or double-strand entities. Chromosomal DNA stability is provided by nucleoprotein-DNA structures termed telomeres [75]. Mammalian telomeres are repetitive DNA sequences, which form a lariat-like structure by associating with the multimeric Shelterin protein complex (also known as the telosome) to shield the exposed ends of chromosomal DNA from damage [76]. Telomeres shorten progressively with each cell replication cycle [77], thus imposing a functional limit on the number of times a cell can safely divide. Significantly shortened telomeres trigger cellular senescence in normal cells, or genomic instability in pre-malignant cells, which contribute to numerous degenerative and aging-related diseases [78]. Multiple lines of research, from human, murine and in cellulo studies, have shown that oxidative stress is associated with accelerated telomere shortening and dysfunction [79][80][81][82]. Several mechanistic models have been proposed to explain how oxidative stress accelerates telomere shortening. Firstly, it has been proposed that oxidative stress triggers cell death and/or senescence, and as a compensation, the extant cells then undergo further recuperative divisions, leading to increased telomere shortening [78]. In addition to this it has been proposed that ROS induce SSBs at telomeres directly, or as intermediates in lesion repair, leading to replication fork collapse and telomere loss [83].

GPCRs - as well as their associated signaling proteins - have been recently the focus of considerable research with respect to their capacity to control signaling activities linked to maintenance of genomic integrity [84][85][86][87]. Interventions linked to GPCR activity have been shown to be associated with classical sites of DNA damage including the aforementioned telomeric sites [88], PARP1 functionality [89] and via the orchestration of multi-protein repair complexes [90]. In addition to these mechanistic intersections between GPCR and DDR mechanisms we have recently identified the G protein-coupled receptor (GPCR) associated protein, GIT2, as a potential keystone in aging [7]. Further work demonstrated that this receptor scaffolding protein also plays a role in oxidative stress responses [91], and is crucial for integrating several components of the DDR [64]. GIT2 knockout (GIT2KO) mice showed an increased vulnerability to DNA damage [64], displayed symptoms of T2DM [92], showed signs of ‘inflammaging’ [65][93] and most importantly, showed accelerated aging compared to their wild-type littermates [65]. While this makes GIT2 an interesting target for treating multiple age-related disorders, GIT2 is a scaffolding protein and is therefore difficult to target directly. Typically, drugs are designed to be directed at enzymes, ion channels or receptors. However, as GIT2 is a GPCR interacting protein, we employed transcriptional profiling to identify a ‘preferred’ GPCR partner for GIT2 signaling and found a strong link with the Relaxin-3 receptor (RXFP3). RXFP3 and GIT2 play similar roles in metabolic aging processes [32]. We also determined the connection between RXFP3 and GIT2 by investigating the role of RXFP3 in oxidative stress and DDR. Analyzing the effects of oxidizing (hydrogen peroxide) and DNA-damaging (camptothecin) stressors on the interacting partners of RXFP3 using Affinity Purification-Mass Spectrometry, we found multiple proteins linked to DDR and cell cycle control. RXFP3 expression increased in response to DNA damage, overexpression, and Relaxin 3-mediated stimulation of RXFP3 reduced phosphorylation of DNA damage marker H2AX, and of the repair protein BRCA1 - both resulting in the attenuation of DNA damage. Our data suggests an RXFP3-GIT2 system that could regulate cellular degradation after DNA damage, and could be a novel mechanism for mitigating the rate of age-related damage accumulation [32]. Hence, GPCR signaling systems may represent multifunctional sensors for DNA damaging insults, and their rational exploitation via novel drug design may facilitate our ability to augment DNA repair processes therapeutically. We proposed that GPCR systems may have long evolved side-by-side with emerging DDR systems to act as sensors, and ameliorative effectors, for intracellular DNA damage and age-related stresses.

2.2.2 GPCRs and cellular senescence

Cellular senescence is a multifaceted process that arrests the proliferation of cells but keeps them from going into an apoptotic state. Cell growth arrest and hyporesponsiveness to extrinsic stimuli via cell surface receptors, such as GPCRs, are hallmarks of senescent cells [94][95][96][97]. Cells that express markers of senescence have been shown to accumulate with age and at sites of certain age-related pathologies. Accumulation of senescent cells can cause local and systemic inflammation, tissue destruction, immune system inhibition and stem and progenitor cell dysfunction [62]. Recent findings

implicate p16-dependent senescence in three components of aging — decrements in neurogenesis, haematopoiesis and pancreatic function [61]. These senescent cells possess distinct functional phenotypes, compared to normal cells, with respect to chromatin remodeling and protein secretory behavior [98][99][100].

Cellular senescence was originally described by Hayflick and Moorhead [101]. An internal factor that can drive cells into replicative senescence is telomeric degradation following each cell cycle [50][102]. The age-associated shortening of telomeres is commonly regarded as an important contributor to organismal aging and considered a powerful biomarker of aging and aging-associated pathological conditions [103]. Since telomeres are necessary to provide stability for the chromosomal DNA [75], telomere attenuation will be strongly associated with DNA frailty [101][104]. Rather than representing a functional ‘dead end’ of cell physiology, evidence gathered over recent years has demonstrated the importance of senescence-related signaling in processes such as embryonic development [105], wound healing/repair [106][107] and, most importantly, aging [108][109].

In addition to telomeric degradation, cellular senescence has been shown to respond to additional stressors. These could be DNA lesions or oxidizing agents (ROS) [110][111], both linked through the DDR signaling pathway. But metabolites, mitochondrial dysfunction and epigenetic changes can also induce growth arrest [50]. The unavoidable accumulation of DNA and oxidative damage, telomere shortening and the impairment of repair mechanisms and immune system function will engender a chronic accumulation of senescent cells over time as an organism grows older [112]. A distinctive feature of senescent cells is the increased expression of cell cycle-inhibitory proteins such as two cyclin-dependent kinase (Cdk) inhibitors, p16 and p21, that are important for senescent cell accumulation during aging. If DNA damage persists, it causes prolonged DDR signaling and protracted proliferative arrest in the form of cellular senescence. Inhibition of DDR signaling kinases like ATM or ATR (ataxia Telangiectasia Rad3 related), allows regulation of senescent cells. These kinases effectively block cell-cycle progression through the stabilization of p53 and transcriptional activation of the cyclin-dependent kinase (Cdk) inhibitor p21 [113][114].

Along with cell cycle arrest, the alteration of the functional cellular ‘secretome’ (i.e., the range of secreted proteins from a specific cell type) of the specific cell entering a senescent state is one of the characteristic features of this aging-associated state [115]. Most senescent cells display profound changes in the chromatin organization which are linked to the cell-autonomous and paracrine aspects of senescence-associated proliferation arrest [113]. Chromatin remodeling causes a coherent cellular response, creating an inflammatory phenotype in which a cell secretes activated interleukins, chemokines, extracellular matrix components, metalloproteinases, growth factors and other signalling molecules [112][116][117]. This modulatory secretory phenotype has now been codified as the senescence-associated secretory phenotype (SASP) [115][118][119]. A small number of senescent cells can cause considerable dysfunction through their SASP phenotype by releasing factors that can cause tissue necrosis, systemic inflammation, stem cell/progenitor dysfunction, fibrosis and spread of senescence to non-senescent cells [62]. SASP activation is a dynamic process that accompanies senescence establishment and can be dependent on DNA damage signaling. DDR can enhance SASP by feed-forward loops that are generated between DDR signaling and ROS attack [119][120]. Interestingly, it has been demonstrated that SASP-associated activity is also strongly linked to modifications in GPCR functionality [113][121][122].

3. Conclusion

While the aging process and the accumulation of age-related damage seem inevitable facts of metabolic life, the strong involvement of GPCR-associated signaling cascades at many levels of this process provides a potentially important and effective drug-based mechanism for amelioration and/or retardation of this process [28][123][124][125]. Aging, as a molecular process, is clearly a slowly developing entity, coordinated by the interaction of multiple signaling systems across almost all somatic tissues over decades. This complexity makes it a troublesome process to target using conventional ‘monolithic target’ therapies, *e.g.* the failure of anti-amyloid therapies targeting age-related dementia [126]. In contrast, complex mechanistic disease systems may be more effectively targeted by therapeutics that possess multidimensional pharmacological efficacy profiles [127][128][129][130]. The discovery and development of the concept that GPCR systems can effectively target and regulate complex transcriptomic/proteomic responses via receptorsome-based non-G protein-dependent signaling [36] provides a feasible platform upon which multidimensional therapeutic interventions for aging can be created [13][28][131]. In their elegant manuscript, Watts and Strogatz [132] demonstrated that an optimal level of communication between entities, within any specific complex system, is facilitated by a level of organization where some nodes within the network possess a greater degree of regulatory connectivity compared to other nodes. In the case of molecular signaling networks in the aging process, it is likely therefore that some proteins possess more profound network-regulating functions than others [7]. These network-controlling factors have been termed ‘keystones’ or ‘hubs’ and are thought to provide a mechanism of dimensional condensation for highly complex cellular signaling systems. This network organization facilitates the rapid transfer of coherent biological/pathological perturbations across a complex series

of nodes by making so-called ‘short cuts’ across the network. As such, the super-complex aging process networks can be controlled at a trophic keystone/hub level rather than by individual sensation/regulation at the individual node (protein or gene) level [92][133]. These keystones therefore likely connect and coordinate multiple discrete signaling cascades that synergize to regulate multifactorial somatic processes. Demonstrating the efficiency of organizing networks in this manner, it has been shown that even networks containing thousands of nodes require only the presence of surprisingly few (5–10) keystones to facilitate rapid transfer across large systems [132]. Targeting these trophic-level proteins, potentially via the recently discovered GPCR-based transcriptomic efficacy role, facilitates regulation of such complex disorders in a rational manner as opposed to the unfeasible proposal of therapeutic aging control at every molecular point in the network [39][131][134][135].

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